Regimen Monograph

A - Regimen Name

COBIVEMU Regimen

Cobimetinib-vemURAfenib

Disease Site

Skin
Melanoma

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For the treatment of patients with previously untreated BRAF V600 mutation-positive unresectable stage III or stage IV melanoma who have a good performance status (ECOG ≤ 2). Brain metastases, if present, should be asymptomatic or stable.

Notes: Data supporting use in patients with BRAF V600K are limited. There are no data to support use of this combination in the treatment of non-cutaneous melanoma, in patients with untreated brain metastases, or in less common BRAF V600 mutations.

Supplementary Public Funding

cobimetinib
Exceptional Access Program (cobimetinib - In combination with vemurafenib for the treatment of patients with previously untreated BRAF V600 mutation-positive unresectable stage III or IV melanoma, according to specific criteria) (EAP Website)

vemURAFenib
Exceptional Access Program (vemURAFenib - In combination with cobimetinib for the treatment of patients with previously untreated BRAF V600 mutation-positive unresectable stage III or stage IV melanoma, with specific criteria) (EAP Website)

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B - Drug Regimen

cobimetinib	60* mg	PO	once daily for 21 days
vemURAFenib	960 mg	PO	BID continuously

*Note: The cobimetinib dose for patients receiving moderate CYP3A4 inhibitors is 20 mg once daily on days 1 to 21.

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Other Supportive Care:

- Patients should be advised to avoid sun exposure (during treatment and for at least 5 days after stopping) and use broad spectrum sunscreen and lip balm (SPF > 30).
- Patients should have a supply of loperamide (initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool; up to a maximum of 16 mg/day) for management at first signs of diarrhea.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Confirmation of BRAF V600 mutation by a validated test is required prior to initiation of treatment.

Dosage with toxicity

The following recommended dose modifications are adapted from the product monographs and the Larkin trial protocol. Refer to individual drug monographs for more information. Dose reduction of each drug is independent of the other drug. Once a dose has been reduced for toxicity, it should not be re-escalated.

Dose level reductions:

Dose level	Cobimetinib	Vemurafenib
-1	40 mg daily	720 mg BID
-2	20 mg daily	480 mg BID
-3	Permanently Discontinue	Permanently Discontinue

Recommended Dose Modifications for Specific Adverse Effects:

Adverse Effect	Severity	Action-Cobimetinib	Action-Vemurafenib
Rhabdomyolysis or symptomatic ↑ CPK or asymptomatic grade 4		Hold for up to 4 weeks*, If recovery to ≤ grade 3; restart at 1 dose level ↓ if clinically indicated.	Continue with no dose reduction.
Asymptomatic ↑ CPK	Grade 3	May continue, or consider hold until ≤ grade 2.	Continue with no dose reduction.
Liver function abnormalities and Hepatotoxicity	Grade 3	Continue with no dose reduction.	Consider hold and 1 dose level ↓.
	First occurrence Grade 4	Hold for up to 4 weeks*, if recovery to ≤ grade 1; restart at 1 dose level ↓.	Hold for up to 4 weeks*, if recovers to ≤ grade 1, restart at 2 dose level ↓.
	Recurrent Grade 4	Permanently discontinue	
Retinal vein occlusion (RVO)	Permanently discontinue		
Serous Retinopathy (including retinal detachment)		Hold for up to 4 weeks*, If recovery to ≤ grade 1; restart at 1 dose level ↓.	Continue with no dose reduction.
Uveitis	Grade ≥ 3	Continue with no dose reduction.	Hold* until ≤ grade 1; restart at 1 dose level ↓.
Photosensitivity	Grade ≤ 2 (tolerable)	Manage with supportive care.	
	Grade 2 (not improved after 7 days with supportive care) (intolerable), Grade ≥ 3	Hold* until ≤ grade 1; restart at previous dose.	Hold* until ≤ grade 1; restart at 1 dose level ↓.
Rash	Grade ≤ 2 (tolerable)	Manage with supportive care.	

		Grade 2 (intolerable) Grade ≥ 3 acneiform rash	Hold until ≤ grade 2; restart at 1 dose level ↓.	Continue with no dose reduction.
		Grade ≥ 3 non-acneiform or maculopapular rash	Continue with no dose reduction.	Hold* until ≤ grade 2; restart at 1 dose level ↓.
		Grade 4 non-acneiform or maculopapular rash	Continue with no dose reduction.	Hold until ≤ grade 2; restart at 2 dose level ↓. If recurs, permanently discontinue.
		SJS/TEN or DRESS	Discontinue if related	Discontinue
	Asymptomatic absolute ↓ in LVEF from baseline > 10% (and < lower limit of normal (LLN))		Hold for 2 weeks; repeat LVEF[1] Restart at 1 dose level ↓ if LVEF ≥ LLN and absolute ↓ from baseline LVEF ≤ 10%. Permanently discontinue if LVEF ≤ LLN, or ↓ from baseline LVEF > 10%.	Continue with no dose reduction
	Symptomatic LVEF ↓ from baseline		Hold for up to 4 weeks; repeat LVEF[1] Consider permanent discontinuation Restart at 1 dose level ↓ if LVEF ≥ LLN and absolute ↓ from baseline LVEF ≤ 10% and symptoms resolve. Permanently discontinue if the symptoms persist, LVEF < LLN, or ↓ from baseline LVEF > 10%.	Continue with no dose reduction; discontinue if grade 3 or 4.
	Hemorrhage	Grade 3	Hold for up to 4 weeks*, if recovers to ≤ grade 1 and clinically appropriate, restart at 1 dose level ↓.	Hold for up to 4 weeks*, if recovers to ≤ grade 1 and clinically appropriate, restart at 2 dose level ↓.

	Grade 4 or cerebral hemorrhage (any grade)	Permanently discontinue	
Any new skin lesions suggestive of cutaneous malignancy		Hold and biopsy; restart at previous dose.	Hold and biopsy; If cuSCC confirmed and excised; restart at previous dose. If not excised: discontinue.

*If not improved within 4 weeks, permanently discontinue
[1]LVEF should be repeated at 2, 4, 10 and 16 weeks after hold

QT Prolongation:

Criteria	Action -Vemurafenib (no action required for cobimetinib)
QTc > 500 ms and > 60 ms ↑ from baseline	Discontinue permanently
QTc > 500 ms during treatment and ≤ 60 ms increase from baseline:	
• 1st occurrence	Hold until QTc < 500 ms. Resume with 1 dose level ↓
• 2nd occurrence	Hold until QTc < 500 ms. Resume with 1 dose level ↓
• 3rd occurrence	Discontinue permanently

Recommended Dose Modifications for Other Adverse Effects:

Severity	Cobimetinib Dose	Vemurafenib Dose
Grade 1 or Grade 2 (tolerable)	No dose reduction; manage symptoms.	No dose reduction; manage symptoms.
Grade 2 (intolerable) or Grade 3 to 4		
1st Appearance	Hold until grade ≤1, restart at 1 dose level ↓.	Hold until grade ≤1, restart at 1 dose level ↓.

2nd Appearance	Hold until grade ≤1, restart at 1 additional dose level ↓.	Hold until grade ≤1, restart at 1 additional dose level ↓.
3rd Appearance	Permanently discontinue	Permanently discontinue

Hepatic Impairment

Hepatic impairment	Cobimetinib	Vemurafenib
Mild to Moderate	No dose adjustment needed	No dose adjustment needed
Severe	No data, use with extreme caution	Use with caution, consider dose reduction

Refer to the dosage with toxicity section for management of hepatic toxicity during treatment.

Renal Impairment

- No dose adjustment of cobimetinib or vemurafenib is recommended in patients with mild or moderate renal impairment.
- The safety and efficacy in patients with severe renal impairment have not been established; use with caution.

Dosage in the Elderly

No dose adjustment is required for either drug.

There was a higher incidence of cobimetinib dose modification (including discontinuation) for adverse events overall in patients ≥ 65 relative to those < 65, specifically for diarrhea, vomiting, asthenia, pyrexia, dehydration, elevated AST, chorioretinopathy, and retinal detachment.

Elderly patients (≥65 years) are at greater risk of experiencing vemurafenib side effects such as cuSCC, decreased appetite and cardiac effects.

Dosage based on Gender:

Gender does not appear to have an effect on cobimetinib exposure.

Women have an increased risk of skin and musculoskeletal toxicity with vemurafenib. Dose modifications are not needed.

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F - Adverse Effects

Refer to cobimetinib, vemURAFenib drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Increased LFT's (may be severe) • Increased CPK (may be severe) • Abnormal electrolytes • Diarrhea • Musculoskeletal pain	• Alopecia • Photosensitivity (may be severe) • Fatigue • Rash (may be severe, includes panniculitis) • Nausea, vomiting • Headache • Secondary malignancy (cutaneous squamous cell carcinoma, basal cell carcinoma) • Fever/chills • Retinopathy, RVD, RVO (maybe severe);	• Anorexia, weight loss • Edema • Hypertension • Myelosuppression • Dysgeusia • Constipation • Hemorrhage • Cough, dyspnea • Ejection fraction decreased • Bleeding (may be severe) • Dizziness • Abdominal pain • Insomnia	• Arrhythmia, atrial fibrillation, prolonged QTc • Cardiotoxicity • Radiation sensitization & recall reaction • Hypersensitivity • Vasculitis • Pneumonitis • Venous thromboembolism • DRESS • Pancreatitis • Tumour lysis syndrome • Dupuytren's contracture • GI obstruction • Seizure • Uveitis • Rhabdomyolysis

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G - Interactions

Refer to cobimetinib, vemURAFenib drug monograph(s) for additional details.

- Avoid concomitant use of cobimetinib with potent or moderate inhibitors of CYP34A.
    - If concomitant short-term (14 days or less) therapy with a moderate CYP3A4 inhibitor is unavoidable, decrease dose of cobimetinib from 60 mg once daily to 20 mg once daily. Resume previous dose when the inhibitor is stopped.
    - For patients taking 40mg daily or less, avoid moderate inhibitors.
- Avoid concomitant use of cobimetinib with potent or moderate inducers of CYP3A4.
- Monitor cobimetinib concentrations if used in combination with drugs that inhibit P-glycoprotein.
- Avoid concomitant use of vemurafenib and drugs that may prolong the QT interval

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H - Drug Administration and Special Precautions

Refer to cobimetinib, vemURAFenib drug monograph(s) for additional details.

Administration

Cobimetinib:

- Tablets should be swallowed whole with a glass of water with or without food.
- Avoid grapefruit, grapefruit juice, and products containing grapefruit extract.
- If a dose is missed and it is more than 12 hours before the next dose, the missed dose should be taken.
- If it is less than 12 hours before the next dose the missed dose should be skipped.
- If a patient vomits after taking a dose, they should not replace the dose that day; treatment should be continued as prescribed the following day.
- Tablets should be stored at room temperature (15-30°C).

Vemurafenib:

- Oral self-administration; drug available by outpatient prescription.
- The daily doses should be given in the morning and in the evening, around 12 hours apart.
- May be administered with or without food, but administration in relation to food should be consistent.
- Film-coated tablet should be swallowed whole with a glass of water; do not crush or split.
- If vomiting occurs after taking a dose, do not take an additional dose. Continue to take the next dose as scheduled.
- If a dose is missed, it may be given if there are more than 4 hours before the next dose. Otherwise, skip this dose and give the next one as scheduled. Never give both doses at the same time.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- Avoid excessive caffeine as this may increase side effects.
- Store between 15-30°C, in the original package; protect from moisture.

Contraindications

- Patients who have a hypersensitivity to cobimetinib or vemurafenib medications or any of the excipients

Other Warnings/Precautions

- Caution must be exercised in patients with:
  - Baseline QTc > 500 ms
  - Wildtype or unknown BRAF status
  - Uncontrolled hypertension (patients were excluded from clinical trials.)
  - Increased QT interval or who are at risk (low potassium/magnesium, congenital QT prolongation, or history of arrhythmia, CHF, anti-arrhythmics, other QTc prolonging agents, prior anthracyclines), diabetes, autonomic neuropathy
  - Prior or concurrent cancers, especially those associated with RAS mutation.
- Avoid concomitant use with strong or moderate CYP3A inhibitor (refer to Interactions section for dose adjustments with moderate inhibitors)
- Concurrent radiation: Radiation sensitization and radiation recall reaction

- Left ventricular dysfunction, hemorrhage (including major hemorrhage), serous retinopathy and retinal vein occlusion were identified in clinical trials
- Risk factors for bleeding, including patients taking concomitant medications that increase risk (i.e. antiplatelets and anticoagulants)
- Not recommended for use in patients with active untreated brain metastases
- Not recommended in patients with decreased LVEF (<50% or below institutional lower limit of normal)
- Not recommended in patients with a history of retinal vein occlusion
- Secondary malignancies (cutaneous squamous cell carcinoma, non-cutaneous squamous cell carcinoma, primary melanoma) are common - patients must be closely monitored and treated appropriately

Pregnancy and Lactation

- Cobimetinib or vemurafenib are not recommended for use in pregnancy. Females of childbearing potential and male patients should use two effective forms of contraception during treatment and for at least **6 months** after treatment cessation.
- Breastfeeding is not recommended with cobimetinib or vemurafenib.
- Fertility effects: Probable (cobimetinib); unknown (vemurafenib).

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- Blood pressure; Baseline and at each visit
- CBC; Baseline and at each visit
- Chest CT scan (for NCuSCC); baseline and every 6 months, until 6 months after the last dose

- Creatinine, CPK levels; Baseline and monthly during treatment, as per institutional guidelines or as clinically indicated. Rule out rhabdomyolysis if CPK increases.
- ECG and electrolytes (including potassium, magnesium and calcium, especially in patients with risk factors for QT prolongation); baseline and after dose modification, Day 15, monthly for first 3 months then every 3 months, or more often as clinically indicated
- Head and neck examination (at least a visual inspection of oral mucosa and lymph node palpation, for NCuSCC); baseline and every 3 months. Also pelvic (females) / anal examinations (for NCuSCC) at baseline, end of treatment and when clinically indicated; all until 6 months after the last dose
- Liver function tests; Baseline and monthly or as clinically indicated during treatment.
- LVEF; Baseline, after the first month of treatment, and at least every 3 months, or as clinically indicated, until treatment discontinuation. Patients restarting treatment with a dose reduction should have LVEF measurements taken at 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated.
- INR in patients taking warfarin; during initiation of vemurafenib and after dose modification or discontinuation
- Clinical toxicity assessment for musculoskeletal, ophthalmic effects, dermatologic effects, bleeding, diarrhea, nausea and vomiting, hypersensitivity, hyperglycemia, pneumonitis, secondary malignancy; Baseline and at each visit. Dermatologic monitoring should continue for 6 months following discontinuation of treatment.
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Outpatient prescription for home administration.

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K - References

Cobimetinib and vemurafenib drug monographs, Cancer Care Ontario.

Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J M ed 2014;371:1867-76.

July 2023 Modified Dose modifications section (for QT prolongation)

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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